REMARKS

Claims 1-29 are pending in the instant application. Claims 1-7, 9-21, 23 and 26-29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 6,103,492 to Yu, in view of United States Patent No. 6,426,058 to Pines et al. Claim 8 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Yu and Pines, and further in view of United States Patent No. 5,834,226 to Maupin. Claim 22 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Yu and Pines, and further in view of United States Patent No. 6,278,893 to Ardenkjaer-Larson et al. Claims 24 and 25 stand rejected under 35 U.S.C. §103(a) as being unpatentable overYu and Pines, and further in view of United States Patent No. 6,110,749 to Obremski. The claims have been amended. Claims 1, 6, and 27 have been amended. Claims 7, 16-19, 21, 22, 28 and 29 have been cancelled. New claims 30 and 31 have been added. Claim 1 now incorporates the limitations of claims 21 and 22. Applicants respectfully submit that none of the amendments constitute new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

Claims 1-7, 9-21, 23 and 26-29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 6,103,492 to Yu, in view of United States Patent No. 6,426,058 to Pines et al. This rejection is respectfully traversed.

Applicants have amended claim 1 to include the limitation of claim 21 and 22, i.e. that hyperpolarization of the NMR active nucleus is achieved either by polarisation transfer using dynamic nuclear polarization or by para-hydrogen-induced-polarization. Thus the method set out in amended claim 1 does not involve the use of a hyperpolarized noble gas since the claimed assay is performed on a biological species using an assay reagent which is either i) introduced as an initial reagent, ii) formed in situ during the assay, or iii) formed as a product of the assay. Applicants note hyperpolarized noble gas is not a biological species and could not be used as an assay reagent because it is chemically inert. Additionally, for the sake of clarity, Applicants have further amended claim 1 to make it clear that the NMR

active nucleus is studied by NMR. Thus, if the NMR active nucleus is ^{13}C, ^{13}C NMR will be used. This is clear from the specification as a whole and in particular from page 6, lines 1-3.

Yu teaches that the interaction of an agent and a receptor can be detected using a number of detection techniques, including spectroscopy (column 40, lines 37-41), which may be NMR (column 41, lines 42-48).

Pines *et al* relates to a method in which the use of a hyperpolarized noble gas is an essential feature. For example, at column 1, in the section headed "Field of the Invention", Pines *et al* states that the invention relates to the use of hyperpolarized noble gases to enhance and improve NMR and MRI. In addition, the whole of the remainder of the description, the claims and the figures of Pines *et al* make it clear that the use of a hyperpolarized noble gas is an essential feature. Thus, although dynamic nuclear polarization is mentioned at column 2 of Pines *et al*, it is made clear in that document that it is intended to be used for the preparation of a hyperpolarized noble gas (column 2, lines 20-37). There is simply no teaching in Pines *et al* of any method that does not include the use of a hyperpolarized noble gas.

Applicants respectfully submit that the presently claimed method, which does not make use of a hyperpolarized noble gas, cannot possibly be obvious in the light of Pines *et al*, in which a hyperpolarized noble gas is essential. Furthermore, Yu does not supply this deficiency.

Moreover, Applicants submit that there would have been no reason for a person of skill in this art to combine the documents as there is no suggestion in Yu that there is any problem with the methods they are describing. Thus, Applicants submit that a person of skill in the art would not be motivated to attempt the hyperpolarization of NMR active nuclei within their assay reagents.

Further still, Applicants submit that there would certainly have been no motivation from Pines for the skilled person to use a hyperpolarization method which does not include the use of a hyperpolarized noble gas. As there would be no motivation to combine the teachings of Pines with Yu, let alone that such a combination would still be insufficient, Applicants respectfully submit that the instant invention is patentably distinct thereover.

With respect to the other references cited by the Examiner:

Applicants respectfully submit that, in accordance with 35 U.S.C. §103(c), United States Patent No. 6,278,893 to Ardenkjaer-Larson et al. is not available as a reference against the present application. First, the Ardenkjaer-Larson patent only qualifies as prior art against the present application under 35 U.S.C. §102(e). Secondly, the present invention was made while under an obligation of assignment to the same entity as the Ardenkjaer-Larson patent. The Ardenkjaer-Larson patent, as shown on its face, was assigned to Nycomed Imaging AS, a division of the instant assignee Nycomed Amersham PLC. Accordingly, the Ardenkjaer-Larson patent is not available to be cited as prior art against the present invention.

Maupin discloses a biological assay that is analyzed at known time intervals so as to allow the determination of reagent concentration. Applicants respectfully submit that Maupin fails to correct the deficiencies of the cited art so as to render the present invention unpatentable.

Obremski teaches an assay which is multiplexed and performed in a multispot assay array. Accordingly, Applicants respectfully submit that Obremski fails to provide the deficiencies of the cited art so as to render the present invention unpatentable.

In view of this, Applicants submit that amended claim 1 is new and non-obvious over the prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 2 and 3 are dependent on claim 1 and are therefore new and non-obvious for the same reasons that amended claim 1 is new and non-obvious. However, Applicants submits that there are also additional reasons for their novelty and non-obviousness over the combination of Yu and Pines *et al.* As the Examiner has pointed out, Yu teaches that the interaction of an agent and a receptor can be detected using a number of detection techniques, inlcuding spectroscopy (column 40, lines 37-41), which may be NMR (column 41, lines 42-48).

Yu also states that isotopically labelled reagents can be used in conjuction with the detection techniques or alone.

However, Applicants respectfully suggest that a careful reading of Yu leads to an interpretation different from that adopted by the Examiner. Yu lists a group of commonly used stable isotopes at column 40, line 45 as follows: ^{2}H, ^{13}C, ^{15}N, ^{18}O. These are clearly intended to be a single category of label which would all be used in the same way. Applicants submits that it is clear that this group of isotopes must simply be intended as labels and not as NMR active nuclei for the reason that ^{18}O has zero spin and is not an NMR active nucleus. Similarly, the list of radioactive isotopes contains both isotopes with zero spin and isotopes with non-zero spin.

Applicants therefore submit that there is no teaching in Yu of the use any of the NMR active nuclei specified in claims 2 and 3 in the detection of an interaction between an agent and a receptor.

Furthermore, Applicants submit that there would have been no reason for a person of skill in this art to combine Yu with Pines *et al* as there is no suggestion in Yu that there is any problem with the methods described.

Claim 4 relates to a method in which the assay reagent contains an artificially high concentration of the NMR active nucleus. The Examiner has said that this feature is taught by Yu since that author has stated that an assay reagent can be isotopically labelled. However, as mentioned above, there is no suggestion that the isotopic label of Yu could be the active nucleus in the NMR analysis and as set out above, Applicants submit that this could not be the case as other isotopes included in the same list are not detectable by NMR.

Claim 5 relates to a method in which the assay reagent contains an artificially high concentration of the NMR active nucleus in up to 10 defined positions. The Examiner has not commented on the clarity of the amended claim but Applicants submit that it is clear to one of skill in the art that the claim refers to the possibility of substituting an atom such as ^{12}C or ^{14}N with a less abundant isotope having non-zero spin such as ^{13}C or ^{15}N at up to 10 positions within the assay reagent molecule. This would not be a difficult matter for a skilled chemist. The substitution would increase the sensitivity of the assay as the number of nuclei viewed by NMR would be increased. The skilled chemist would be able to select the most suitable positions for the substitution on the basis of the particular assay being carried out.

Applicants have inserted a new claim 30 which is dependent on claim 5 and which specifies that there is an artificially high concentration of the NMR active nucleus at one specific position. Basis for this claim can be found at page 3, lines 30-31 of the specification.

Applicants submit that both claim 5 and new claim 30 are non-obvious over all of the cited documents. There is no teaching in Yu of substituting a non-NMR active nucleus for an NMR active nucleus and certainly no suggestion that the position of the substitution could be carefully selected so as to increase the sensitivity of the assay. The only use of the isotopic labels that seems to be suggested by Yu is to attach them somewhere in the assay reagent so that they can be detected in some unspecified way.

The Examiner has objected that claim 6 is obvious over the combined teaching of Yu and Pines *et al* and draws Applicant's attention to the competitive displacement assay

described in Yu at column 55, lines 54-56. However, Applicants submit that this claim is not obvious because it depends on a non-obvious claim 1.

Applicants have amended claim 6 to read as follows:

> The method of claim 1, wherein the assay reagent is an organic compound comprising an NMR active nucleus located at the site of a chemical bond which is broken during the course of the assay.

Basis for this amendment can be found at page 16, lines 11-17. The amendment further distinguishes the claim from the competitive displacement assay described by Yu at column 55, lines 54-56 because there is no disclosure in Yu of such an assay in which an NMR active nucleus is positioned at the site where the bond is broken. Indeed, in a displacement assay, this would be difficult to do since there is generally more than one site of interaction between a receptor and a receptor binding compound.

Claim 7 has been deleted and replaced by new claim 31 which reads as follows:

> The method of claim 1 wherein the assay reagent the assay reagent is an organic compound comprising two or more NMR active nuclei associated with a chemical bond which is broken during the course of the assay such that when the bond is intact, the said NMR active nuclei are spin coupled and when the bond is broken the spin coupling is disrupted.

Basis for this claim can be found at page 16, lines 17-24, which explains that spin coupling occurs when two NMR active nuclei are in approximate proximity and is disrupted when they are separted, for example by the breaking of a bond.

There is no teaching anywhere in the Yu citation of an analyte containing two spin coupled NMR active nuclei and Applicants therefore submit that claim 7 is not obvious over the cited prior art.

Claim 8 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Yu and Pines, and further in view of United States Patent No. 5,834,226 to Maupin. This rejection is respectfully traversed.

The Examiner has objected that claim 8 is obvious over Yu and Pines *et al* further in view of Maupin. Applicants previously argued that Maupin was not relevant to the present application because it does not relate to an assay in which a physical or chemical change in a biological species is monitored by NMR. The Examiner has asserted in reply that Maupin is relevant in teaching the analysis of biological assays.

Firstly Applicants assert that claim 8 is new and non-obvious by reason of its dependence on amended claim 1. However, Applicants submit that there are additional reasons for its novelty and non-obviousness. Although as the Examiner has pointed out, Maupin illustrates the principle of monitoring the progress of a biological assay, Applicants submit firstly that the assay of Maupin could not have been monitored by NMR and secondly that one of skill in the art would have believed that it would have been difficult to apply the principles of Maupin to an assay monitored by NMR because of the problem of sensitivity which is solved by the method of the present invention. Therefore, claim 8 is patentably distinct over the prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 9 to 15 are dependent on claim 1 and rely for their patentability on claim 1.

Claims 16 to 19 and 23 have been deleted for consistency with the amendment to claim 1.

Applicants submit that claim 20 is new and non-obvious through its dependence on new and non-obvious claim 1.

Claims 21 and 22 have also been deleted as their subject matter has been incorporated into claim 1.

Claim 22 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Yu and Pines, and further in view of United States Patent No. 6,278,893 to Ardenkjaer-Larson et al. Applicants respectfully submit that this rejection stands traversed as the Ardenkjaer-Larson patent has been removed from consideration against the instant application.

Claims 24 and 25 stand rejected under 35 U.S.C. §103(a) as being unpatentable overYu and Pines, and further in view of United States Patent No. 6,110,749 to Obremski. This rejection is respectfully traversed.

Applicants respectfully submit that as claims 24 and 25 depend from allowable claim 1, each is likewise patentably distinct over the prior art. Reconsideration and withdrawal of the rejections are respectfully requested.

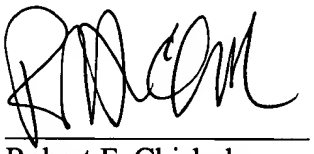
Claim 27 is dependent on claim 1 and is therefore new and non-obvious.

Claims 28 and 29 have been deleted.

In view of the amendments and remarks hereinabove, Applicants respectfully submit that the present application, including claims 1-6, 8-27, and 30-31, is in condition for allowance. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicants' undersigned counsel at the telephone number below.

Respectfully submitted,



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